OCULAR TREATMENT

This is a division of application Ser. No. 07/299,689, filed Jan. 23, 1989, now U.S. Pat. No. 4,952,212, filed 8/20/90 which is a Rule 60 continuation of application Ser. No. 06/929,476, filed 11/12/86.

The present invention relates to a process of ocular treatment, to formulations useful in such a process and to apparatus suitable for applying such formulations.

A conventional method of ocular administration of a pharmacologically active substance comprises the use of eye drops. This is generally known to have low patient acceptability, especially in the young. The administration of a large drop of liquid to the eye initiates a blink reflex which can cause substantial wastage of an applied active substance by drainage either through the tear ducts or on the skin surface. Indeed it has been reported that if a 30–50 μl drop is applied to the eye the actual volume that reaches the target is 5–7 μl. Therefore, in addition to the low patient acceptability, there is a 4–10 fold wastage. This leads to an inefficiency in the use of expensive ingredients and, in addition, the administrator has little control, and is uncertain, over the amount of ingredient applied to the target.

Another conventional method of ocular administration of an active ingredient comprises the use of an ointment. This similarly has been found to have low patient acceptability and substantial wastage of active ingredient can result.

The present invention provides a solution to these problems of the art by providing accurate dispensing of a low volume of a pharmacologically active substance to the eye. This is achieved by a process which involves electrodynamic spraying of a suitable formulation by raising the formulation to a high potential in a spray nozzle to cause the formulation to atomise as a spray of electrically charged droplets. Such electrically charged droplets seek the closest earthed object to discharge their electric charge, and this can be arranged to be the target area of the eyeball, more particularly the cornea. This process provides a particularly even, accurately targetted, coating of the eye with the formulation.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a side schematic view of principal components of one embodiment of the apparatus of the invention;

FIG. **2** is a side schematic view of the principal components of a multi-dose embodiment of the apparatus of the invention;

FIG. **3** shows a top view of a camera and optical system suitable for use in recording mydriasis resulting from the topical application of the formulation of the invention to the eye; and

FIGS. **4** and **5** are graphical representations of mean differences (with standard error bars) in percentage change between the test and control eyes for indicated time points.

Accordingly, the present invention provides a method of administering to an eye a formulation comprising an ophthalmically active substance and an ophthalmically acceptable diluent, characterised in that the formulation has a viscosity in the range 10^{-3} to 1.0 Pa.s (at 25° C.) and a resistivity in the range 10^4 to 10^{12} ohm cm (at 25° C.), and that the formulation is supplied to a spray nozzle wherein a sufficiently large electrical potential, relative to earth, is applied to the formulation from a high voltage generator, that a sufficient electrical gradient is provided at the nozzle to atomise the formulation as a spray of electrically charged droplets.

The method of the invention may be carried out in a unit dose mode, by charging the nozzle with a unit dose from an external source each time it is used, or in a multi-dose mode, in which case a reservoir of the formulation supplies a unit dose automatically to the spray nozzle each time the method is carried out.

In another aspect the present invention provides a liquid solution formulation comprising an ophthalmically active substance and an ophthalmically acceptable diluent which comprises 50% to 100% by weight of an ophthalmically acceptable organic diluent, and from 0% to 50% by weight of water, and has a viscosity in the range 10^{-3} to 1.0 Pa.s at 25° C. and a resistivity in the range 10^4 to 10^{12} ohm cm at 25° C.

A suitable such diluent may be a mixture of two or more liquid components.

The ophthalmically active substances encompassed by this invention are any compounds having a pharmacological effect on and/or in the eye. Typical of such compounds are chemotherapeutic agents, compounds to aid ocular examination and compounds to aid surgery; for example

(a) anti-inflammatory agents, such as prednisolone and other corticosteroids;
(b) antimicrobial drugs, such as antibiotics, antiseptics, antivirals, fungicides and sulphonamides, for example chloramphenicol, sulphacetamide, gentamycin, nystatin, acyclovir and idoxuridine;
(c) autonomic drugs, such as β-adrenoceptor antagonists, cycloplegics, miotics, mydriatics and vasoconstrictors, for example timolol, atenolol, pilocarpine, atropine, tropicamide, hyoscine, ephedrine, phenylephrine, carbachol, guanethidine and adrenaline;
(d) local anaesthetics, such as lignocaine or oxybuprocaine;
(e) diagnostics, such as fluorescein;
(f) drugs to assist healing of corneal abrasions, such as urogastrone and epidermal growth factor (EGF);
(g) drugs of use in diabetic retinopathy, such as aldose reductase inhibitors, for example sorbinil and 3-(4-bromo-2-fluorobenzyl)-4-oxo-3H-phthalazin-1-ylacetic acid;

of which (c) is the most important group, and (f) and (g) are also particularly important.

As hereinbefore discussed, conventional methods of ocular administration lead to wastage of ingredient for example by drainage through the naso-lachrymal duct into the throat, and subsequent ingestion into the gastro-intestinal tract, whence it can be absorbed systemically, and exert undesired side-effects. For example, it is well documented in the literature that β-adrenoceptor antagonists administered as eye-drops can exert a significant cardiovascular effect, as a result of such ingestion into the gastro-intestinal tract.

The present invention enables accurate targetting of a fine spray of electrically charged particles of the formulation to dose the required amount, thereby substantially eliminating unwanted side-effects.

The formulation may not be predominantly aqueous as it has been found that aqueous formulations do not undergo electrodynamic spraying satisfactorily due to their high conductivity. Preferably, the amount of water, if any is present, comprises not more than about 20% by weight of the total diluent, and preferably less than 10% by weight.